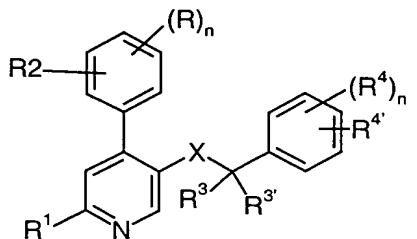


Claims:

1. A compound of the formula



wherein

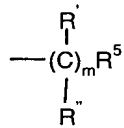
R is hydrogen or halogen;

R<sup>1</sup> is  $-(C\equiv C)_mR^{1'}$  or  $-(CR'=CR'')_mR^{1'}$

wherein R<sup>1'</sup> is

a) hydrogen or halogen,

b) cyano, or the following groups:



c) ,

d)  $-C(O)NR'R''$ ,

e)  $-C(O)O(CH_2)_mR^5$ ,

f)  $-C(O)R^5$ ,

g)  $-N(OH)-(CH_2)_mR^5$ ,

h)  $-NR'C(O)-(CH_2)_mR^5$ ,

i)  $-N[C(O)-R']_2$ ,

j)  $-OR^6$ ,

k)  $-(CH_2)_m-SR^6$ ,  $-(CH_2)_m-S(O)R^6$ , or  $-(CH_2)_m-S(O)_2R^6$ ,

l) aryl, unsubstituted or substituted by one or more substituents, selected from halogen,

trifluoromethyl, lower alkyl, lower alkoxy, cyano, hydroxy,  $-NR'R''$ , nitro,

$-(CH_2)_nOR'$ ,  $-C(O)NR'R''$ ,  $-C(O)OR'$  or  $-C(O)R'$ ,

m) is a five or six membered aromatic heterocycle, containing one to four heteroatoms,

selected from N, O or S and, unsubstituted or substituted by one or more

Sub  
~~AB~~



Year	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100
1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	

$R^4/R^4'$  are hydrogen, halogen,  $CF_3$ , lower alkyl or lower alkoxy;

$R$  and  $R^2$  or  $R^4$  and  $R^4'$  may be together  $-CH=CH-CH=CH-$ , unsubstituted or substituted by one or two substituents selected from lower alkyl, halogen or lower alkoxy;

$X$  is  $-C(O)N(R^8)-$ ,  $(CH_2)_pO-$ ,  $-(CH_2)_pN(R^8)-$ ,  $-N(R^8)C(O)-$  or  $-N(R^8)-(CH_2)_p-$ ; wherein  $R^8$  is hydrogen or lower alkyl;

$n$  is 1 or 2;

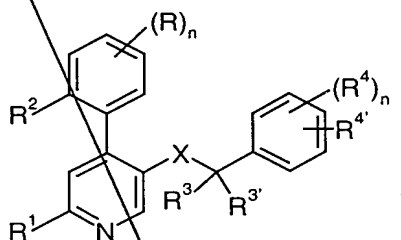
$m$  is 0, 1, 2, 3 or 4;

$o$  is 1 or 2; and

$p$  is 1 or 2;

or a pharmaceutically acceptable acid addition salt thereof.

2. A compound of the formula



wherein

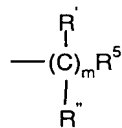
$R$  is hydrogen or halogen;

$R^1$  is  $-(C\equiv C)_mR^{1'}$  or  $-(CR'=CR'')_mR^{1'}$

wherein  $R^{1'}$  is

a) halogen,

b) cyano, or the following groups:



c)

d)  $-C(O)NR'R''$ ,

e)  $-C(O)O(CH_2)_mR^5$ ,

f)  $-C(O)R^5$ ,

g)  $-N(OH)-(CH_2)_mR^5$ ,

h)  $-NR'C(O)-(CH_2)_mR^5$ ,

i)  $-N[C(O)-R']_2$ ,

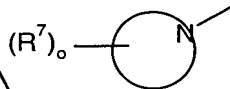
j)  $-OR^6$ ,

k)  $-SR^6$ ,  $-S(O)R^6$ , or  $-S(O)_2R^6$ ,

l) aryl, unsubstituted or substituted by at least one substituent, selected from halogen, trifluoromethyl, lower alkyl, lower alkoxy, cyano, hydroxy,  $-NR'R''$ , nitro,  $-(CH_2)_nOR'$ ,  $-C(O)NR'R''$ ,  $-C(O)OR'$  or  $-C(O)R'$ ,

m) is a five or six membered heteroaryl group, containing one to four heteroatoms, selected from N, O or S and is unsubstituted or substituted by at least one substituent, selected from halogen, trifluoromethyl, lower alkyl, lower alkoxy, cyano, hydroxy,  $-NR'R''$ , nitro,  $-(CH_2)_nOR'$ ,  $-C(O)OR'$ ,  $-C(O)NR'R''$  or  $-C(O)R'$ ,

n) is a five or six membered non-aromatic heterocycle of the formula



or a five or six membered non-aromatic heterocycle containing one additional heteroatom, selected from N, O or S,

$R'/R''$  are hydrogen, lower alkyl, cycloalkyl or aryl,

unsubstituted or substituted by at least one substituent, selected from halogen, trifluoromethyl, lower alkyl, lower alkoxy, cyano, hydroxy,  $-NR'''R''''$ , nitro,  $-(CH_2)_nOR'''$ ,  $-C(O)NR'''R''''$ ,  $-C(O)OR'''$  or  $-C(O)R'''$ ,

$R'''/R''''$  are independently from each other hydrogen, lower alkyl, cycloalkyl or aryl,

$R^5$  is hydrogen, cyano, hydroxy, halogen, trifluoromethyl,  $-C(O)OR'$  or aryl, unsubstituted or substituted by at least one substituents, selected from halogen, trifluoromethyl, lower alkyl, lower alkoxy, cyano, hydroxy,  $-NR'R''$ , nitro,  $-(CH_2)_nOR'$ ,  $-C(O)NR'R''$ ,  $-C(O)OR'$  or  $-C(O)R'$ , or is a five or six membered

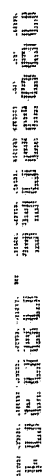
heteroaryl group, containing one to four heteroatoms, selected from N, O or S and is unsubstituted or substituted by at least one substituents, selected from

halogen, trifluoromethyl, lower alkyl, lower alkoxy, cyano, hydroxy,  $-NR'R''$ , nitro,  $-(CH_2)_nOR'$ ,  $-C(O)NR'R''$ ,  $-C(O)OR'$  or  $-C(O)R'$ ,

$R^6$  is hydrogen, lower alkyl, trifluoromethyl, or aryl,

unsubstituted or substituted by at least one substituents, selected from halogen,

Sub  
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[illegible][illegible][illegible][illegible][illegible][illegible][illegible][illegible][illegible][illegible][illegible][illegible][illegible][illegible]

Sub A1  
-N[C(O)-cycloalkyl]<sub>2</sub>, -N(R)C(O)-(CH<sub>2</sub>)<sub>m</sub>OH, pyridin-2,3,4-yl or phenyl, unsubstituted or substituted by lower alkyl, lower alkoxy or hydroxy or is morpholinyl or piperazinyl, substituted by -C(O)-(CH<sub>2</sub>)<sub>m</sub>OH or oxy group(s),

R is hydrogen or lower alkyl;

R<sup>2</sup> is lower alkyl or halogen;

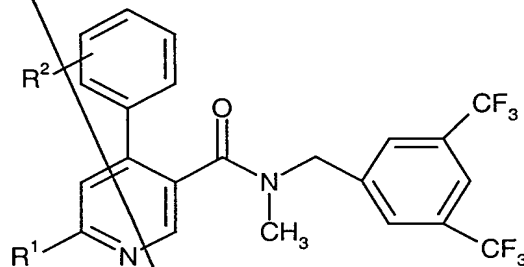
R<sup>3</sup>/R<sup>3'</sup> are hydrogen or lower alkyl;

X is -C(O)N(R<sup>8</sup>)- or -N(R<sup>8</sup>)C(O)-;

R<sup>8</sup> is hydrogen or lower alkyl; and

m is 1 or 2.

4. A compound according to claim 1 having the formula



wherein R<sup>1</sup> and R<sup>2</sup> are as defined above.

5. A compound according to claim 4, further comprising R<sup>2</sup> being lower alkyl.

6. A compound according to claim 5 further comprising R<sup>2</sup> being 2-methyl.

7. A compound according to claim 6 further comprising R<sup>1</sup> being an unsubstituted or substituted five or six membered non-aromatic heterocycle containing at least one nitrogen or one nitrogen and one additional hetero atom selected from the group N, O or S.

8. A compound according to claim 7 wherein the compound is N-(3,5-bis-trifluoromethyl-benzyl)-6-(4-hydroxyacetyl-piperazin-1-yl)-N-methyl-4-o-tolyl-nicotinamide.

- Sch  
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9. A compound according to claim 7 wherein the compound is 4-o-tolyl-1',2',3',6'-tetrahydro-[2,4']bipyridinyl-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide.
10. A compound according to claim 6 further comprising R<sup>1</sup> being aryl substituted by at least one substituent.
11. A compound according to claim 10 wherein the compound is N-(3,5-bis-trifluoromethyl-benzyl)-6-(4-methoxy-phenyl)-N-methyl-4-o-tolyl-nicotinamide.
12. A compound according to claim 10 wherein the compound is N-(3,5-bis-trifluoromethyl-benzyl)-6-(4-hydroxymethyl-phenyl)-N-methyl-4-o-tolyl-nicotinamide.
13. A compound according to claim 6 further comprising R<sup>1</sup> being a five or six member hetero aryl group containing one to four heteroatoms substituted by at least one substituent.
14. A compound according to claim 13 wherein the compound is 2'-methyl-4-o-tolyl-[2,4']bipyridinyl-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide.
15. A compound according to claim 13 wherein the compound is N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-6-(3-methyl-[1,2,4]oxadiazol-5-yl)-4-o-tolyl-nicotinamide
16. A compound according to claim 6 further comprising R<sup>1</sup> being unsubstituted hetero aryl.
17. A compound according to claim 16 wherein the compound is 4-o-tolyl-[2,4']bipyridinyl-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide.
18. A compound according to claim 16 wherein the compound is 4-o-tolyl-[2,3']bipyridinyl-5-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methyl-amide.
19. A compound according to claim 6 further comprising R<sup>1</sup> being cyano.
20. A compound according to claim 19 wherein the compound is N-(3,5-bis-trifluoromethyl-benzyl)-6-cyanomethyl-N-methyl-4-o-tolyl-nicotinamide.
21. A compound according to claim 6 further comprising R<sup>1</sup> being -(CH<sub>2</sub>)<sub>m</sub>-S(O)R<sup>6</sup>.

22. A compound according to claim 21 wherein the compound is (RS)-N-(3,5-bis-trifluoromethyl-benzyl)-6-(2-hydroxy-ethanesulfinylmethyl)-N-methyl-4-o-tolyl-nicotinamide.

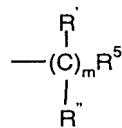
23. A compound according to claim 21 wherein the compound is (RS)-N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-6-(pyridine-2-sulfinyl)-4-o-tolyl-nicotinamide.

24. A compound according to claim 6 further comprising  $R^1$  being  $-OR^6$ .

25. A compound according to claim 24 wherein the compound is N-(3,5-bis-trifluoromethyl-benzyl)-6-hydroxymethyl-N-methyl-4-o-tolyl-nicotinamide.

26. A compound according to claim 24 wherein the compound is N-(3,5-bis-trifluoromethyl-benzyl)-6-(3-hydroxy-propoxy)-N-methyl-4-o-tolyl-nicotinamide.

27. A compound according to claim 6 further comprising  $R^1$  being



wherein  $R'$ ,  $R''$ ,  $R^5$  and  $m$  are as above.

28. A compound according to claim 27 wherein the compound is N-(3,5-bis-trifluoromethyl-benzyl)-6-(3-cyano-propyl)-N-methyl-4-o-tolyl-nicotinamide.

29. A compound according to claim 6 further comprising  $R^1$  being  $-(CH_2)_m-SR^6$ , and  $m$  is as above.

30. A compound according to claim 29 wherein the compound is N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-6-(1-methyl-1H-imidazol-2-ylsulfanylmethyl)-4-o-tolyl-nicotinamide.



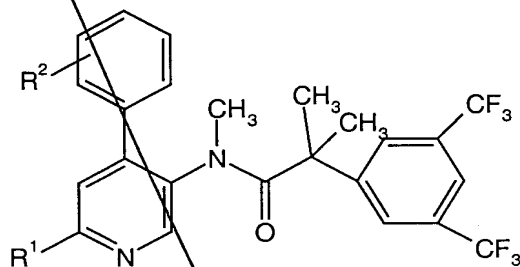
31. A compound according to claim 6 further comprising  $R^1$  being  $-(CH_2)_m-S(O)_2R^6$ , with  $m$  and  $R^6$  as above.

32. A compound according to claim 31 wherein the compound is N-(3,5-bis-trifluoromethyl-benzyl)-N-methyl-6-(pyridine-2-sulfonyl)-4-o-tolyl-nicotinamide.

33. A compound according to claim 4 further comprising  $R^1$  and  $R^2$  being halogen.

34. A compound according to claim 33 wherein the compound is N-(3,5-bis-trifluoromethyl-benzyl)-6-chloro-4-(4-fluoro-phenyl)-N-methyl-nicotinamide.

35. A compound according to claim 1 having the structure



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wherein  $R^1$  and  $R^2$  are as above.

36. A compound according to claim 35 further comprising  $R^1$  being halogen.

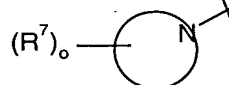
37. A compound according to claim 36 wherein said halogen is chlorine.

38. A compound according to claim 37 wherein the compound is 2-(3,5-bis-trifluoromethyl-phenyl)-N-(6-chloro-4-o-tolyl-pyridin-3-yl)-N-methyl-isobutyramide.

39. A compound according to claim 35 further comprising  $R^2$  being halogen.

40. A compound according to claim 39 wherein said halogen is 2-chloro.

41. A compound according to claim 40 wherein the compound is 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-[hydroxy-(2-hydroxy-ethyl)-amino]-pyridin-3-yl]-N-methyl-isobutyramide.
42. A compound according to claim 40 wherein the compound is 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-6-(3-oxo-morpholin-4-yl)-pyridin-3-yl]-N-methyl-isobutyramide.
43. A compound according to claim 40 wherein the compound is 2-(3,5-bis-trifluoromethyl-phenyl)-N-[4-(2-chloro-phenyl)-2'-methyl-[2,4']bipyridinyl-5-yl]-N-methyl-isobutyramide.
44. A compound according to claim 35 further comprising  $R^2$  being lower alkyl.
45. A compound according to claim 44 wherein  $R^2$  is methyl.
46. A compound according to claim 45 wherein  $R^1$  is  $-NR'C(O)-(CH_2)_mR^5$  and  $R'$ ,  $R^5$  and  $m$  are as above.
47. A compound according to claim 46 wherein the compound is acetic acid (5-[[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino]-4-o-tolyl-pyridin-2-ylcarbamoyl)-methyl ester.
48. A compound according to claim 46 wherein the compound is 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(2-hydroxy-acetyl-amino)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide.
49. A compound according to claim 46 wherein the compound is 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(hydroxyacetyl-methyl-amino)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide.
50. A compound according to claim 45 further comprising  $R^1$  being a five or six membered non-aromatic heterocycle of the formula



or a five or six membered non-aromatic heterocycle containing one additional heteroatom, selected from N, O or S and wherein  $R^7$  and o are as above.

51. A compound according to claim 50 wherein the compound is 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(2,5-dioxo-pyrrolidin-1-yl)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide.

52. A compound according to claim 50 wherein the compound is 2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(3-oxo-morpholin-4-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide.

53. A compound according to claim 45 further comprising  $R^1$  being  $-N[C(O)-R']_2$  and wherein  $R'$  is as above.

54. A compound according to claim 53 wherein the compound is cyclopropanecarboxylic acid (5-{[2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridin-2-yl)-cyclopropanecarbonyl-amide.

55. A compound according to claim 45 further comprising  $R^1$  being  $-N(OH)-(CH_2)_mR^5$ , wherein  $R'$ , m and  $R^5$  are as above.

56. A compound according to claim 55 wherein the compound is 2-(3,5-bis-trifluoromethyl-phenyl)-N-{6-[hydroxy-(2-hydroxy-ethyl)-amino]-4-o-tolyl-pyridin-3-yl}-N-methyl-isobutyramide.

57. A compound according to claim 45 further comprising  $R^1$  being  $-(C\equiv C)_mR^{1'}$  and wherein m and  $R^{1'}$  are as above.

58. A compound according to claim 57 wherein the compound is 2-(3,5-bis-trifluoromethyl-phenyl)-N-(6-ethynyl-4-o-tolyl-pyridin-3-yl)-N-methyl-isobutyramide.

59. A compound according to claim 57 wherein the compound is 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(3-hydroxy-prop-1-ynyl)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide.
60. A compound according to claim 45 further comprising  $R^1$  being  $-C(O)O(CH_2)_mR^5$  and wherein m and  $R^5$  are as above.
61. A compound according to claim 60 wherein the compound is 5-{{2-(3,5-bis-trifluoromethyl-phenyl)-2-methyl-propionyl]-methyl-amino}-4-o-tolyl-pyridine-2-carboxylic acid methyl ester.
62. A compound according to claim 45 further comprising  $R^1$  being  $-OR^6$  and wherein  $R^6$  is as defined above.
63. A compound according to claim 62 wherein the compound is 2-(3,5-bis-trifluoromethyl-phenyl)-N-(6-hydroxy-4-o-tolyl-pyridin-3-yl)-N-methyl-isobutyramide.
64. A compound according to claim 45 further comprising  $R^1$  being  $-(CH_2)_m-S(O)R^6$  and wherein m and  $R^6$  are as defined above.
65. A compound according to claim 64 wherein the compound is (RS)-2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(3-methoxy-benzenesulfinyl)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide.
66. A compound according to claim 45 further comprising  $R^1$  being a five or six membered aromatic heterocycle, containing one to four heteroatoms, selected from N, O or S and, unsubstituted or substituted by one or more substituents, selected from halogen, trifluoromethyl, lower alkyl, lower alkoxy, cyano, hydroxy,  $-NR'R''$ , nitro,  $-(CH_2)_nOR'$ ,  $-C(O)OR'$ ,  $-C(O)NR'R''$  or  $-C(O)R'$ , and wherein n,  $R'$  and  $R''$  are as above.

67. A compound according to claim 67 wherein the compound is 2-(3,5-bis-trifluoromethyl-phenyl)-N-[6-(3-hydroxymethyl-isoxazol-5-yl)-4-o-tolyl-pyridin-3-yl]-N-methyl-isobutyramide.

68. A method of alleviating the symptoms of patient having a disease state treatable by modulation of NK-1 receptor antagonists comprising administering an effective amount of a medicament containing a sufficient quantity of the compound of claim 1.

69. A medicament containing a compound of claim 1 and at least one pharmaceutically acceptable excipient

70. A medicament according to ~~claim~~ 69 for the treatment of diseases related to NK-1 receptor antagonists.

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